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attachment to Paper #28

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  *              W E L C O M E   T O   T H E                  *
  *         U. S.   P A T E N T   T E X T   F I L E           *
  *                                                           *
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=> s adenovir? and vector? and protein IX

          2652 ADENOVIR?
         65103 VECTOR?
         60184 PROTEIN
         64640 IX
           205 PROTEIN IX
                 (PROTEIN(W)IX)
L1          38 ADENOVIR? AND VECTOR? AND PROTEIN IX

=> s l1 and E1a

           311 E1A
L2           1 L1 AND E1A

=> d l1,1-38,cit


1.  5,741,772, Apr. 21, 1998, Neurotrophic factor NNT-1; Ming-shi Chang,
514/2; 530/300, 350 [IMAGE AVAILABLE]

2.  5,733,771, Mar. 31, 1998, cDNAs encoding minor ampullate spider silk
proteins; Randolph V. Lewis, et al., 435/252.3; 530/350; 536/23.5 [IMAGE
AVAILABLE]

3.  5,728,810, Mar. 17, 1998, Spider silk protein; Randolph V. Lewis, et
al., 530/353, 350 [IMAGE AVAILABLE]

4.  5,728,520, Mar. 17, 1998, Immunoreactive polypeptide compositions;
Amy J. Weiner, et al., 435/5; 530/350 [IMAGE AVAILABLE]

5.  5,719,266, Feb. 17, 1998, Anti-obesity proteins; Richard D. DiMarchi,
et al., 530/350, 324 [IMAGE AVAILABLE]

6.  5,714,589, Feb. 3, 1998, Method of selectively extracting osteogenic
protein; Hermann Oppermann, et al., 530/413; 435/7.1; 530/326, 327, 328,
350, 387.9, 395, 840 [IMAGE AVAILABLE]

7.  5,712,143, Jan. 27, 1998, Flea protease proteins, nucleic acid
molecules, and uses thereof; Robert B. Grieve, et al., 435/212;
424/265.1; 514/830; 530/413 [IMAGE AVAILABLE]

8.  5,707,618, Jan. 13, 1998, Adenovirus vectors for gene
therapy; Donna Armentano, et al., 424/93.21, 93.2; 435/172.3, 320.1;
514/44 [IMAGE AVAILABLE]

9.  5,705,611, Jan. 6, 1998, Human GM-CSF receptor component; Kazuhiro
Hayashida, et al., 530/350; 435/69.1; 536/23.5 [IMAGE AVAILABLE]

10.  5,705,151, Jan. 6, 1998, Gene therapy for T cell regulation; Steve
W. Dow, et al., 424/93.21, 450; 435/7.2, 69.1, 172.3, 320.1; 514/44;
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935/54, 55, 62, 71 [IMAGE AVAILABLE]

11. 5,700,638, Dec. 23, 1997, Cell death regulator; Stanley J. Korsmeyer, 435/6, 7.1, 7.2, 7.21, 7.31, 7.8, 69.1, 172.3; 436/501; 530/350 [IMAGE AVAILABLE]

12. 5,691,179, Nov. 25, 1997, Cell death regulators; Stanley J. Korsmeyer, 435/355, 172.3, 252.3, 254.11, 320.1, 325, 372, 372.2; 536/23.5, 24.31 [IMAGE AVAILABLE]

13. 5,670,488, Sep. 23, 1997, **Adenovirus vector** for gene therapy; Richard J. Gregory, et al., 514/44; 424/93.2; 435/320.1; 935/62 [IMAGE AVAILABLE]

14. 5,670,153, Sep. 23, 1997, Immunoreactive polypeptide compositions; Amy J. Weiner, et al., 424/189.1, 228.1; 435/5; 530/350 [IMAGE AVAILABLE]

15. 5,670,152, Sep. 23, 1997, Immunoreactive polypeptide compositions; Amy J. Weiner, et al., 424/189.1, 228.1; 435/5; 530/350 [IMAGE AVAILABLE]

16. 5,658,882, Aug. 19, 1997, Methods of inducting formation of tendon and/or ligament tissue comprising administering BMP-12, BMP-13, and/or MP-52; Anthony J. Celeste, et al., 514/12; 435/69.1, 252.3, 320.1, 375; 514/2, 8; 530/350, 399; 536/23.4, 23.5 [IMAGE AVAILABLE]

17. 5,652,223, Jul. 29, 1997, DNA encoding CAI resistance proteins and uses thereof; Elise C. Kohn, et al., 514/44; 435/91.1, 91.5, 172.3, 320.1; 536/23.1, 23.2, 23.5; 935/9, 14 [IMAGE AVAILABLE]

18. 5,652,123, Jul. 29, 1997, Protein having interleukin 13 activity, recombinant DNA coding for this protein, transformed cells and microorganisms; Daniel Caput, et al., 435/69.52; 424/85.2; 435/252.33, 254.2, 320.1, 325, 358, 360, 365.1; 530/351; 536/23.5 [IMAGE AVAILABLE]

19. 5,646,115, Jul. 8, 1997, Ectoparasite saliva proteins and apparatus to collect such proteins; Glenn R. Frank, et al., 514/12; 424/185.1, 275.1; 530/300, 324, 858 [IMAGE AVAILABLE]

20. 5,641,875, Jun. 24, 1997, DNA encoding chimeric IgG Fc receptor; Alan D. Schreiber, et al., 536/23.4; 435/69.7, 252.3, 320.1; 530/350 [IMAGE AVAILABLE]

21. 5,641,863, Jun. 24, 1997, Chimeric IgG Fc receptors; Alan D. Schreiber, et al., 530/350; 435/69.7; 536/23.7 [IMAGE AVAILABLE]

22. 5,606,029, Feb. 25, 1997, Gene for a growth factor and its cDNA and protein; Sandra J. Degen, 530/399; 536/23.5 [IMAGE AVAILABLE]

23. 5,605,690, Feb. 25, 1997, Methods of lowering active TNF-.alpha. levels in mammals using tumor necrosis factor receptor; Cindy A. Jacobs, et al., 424/134.1; 435/69.7; 514/12, 825; 530/350, 387.3, 866, 868 [IMAGE AVAILABLE]

24. 5,604,201, Feb. 18, 1997, Methods and reagents for inhibiting furin endoprotease; Gary Thomas, et al., 514/12; 435/252.3, 254.2, 320.1; 530/350; 536/23.5 [IMAGE AVAILABLE]

25. 5,595,904, Jan. 21, 1997, Family of map2 protein kinases; Teri G. Boulton, et al., 435/325, 243, 252.8, 254.2, 320.1, 348, 353; 536/23.5 [IMAGE AVAILABLE]

26. 5,594,101, Jan. 14, 1997, Anti-obesity proteins; Gerald W. Becker, et al., 530/317, 324, 350 [IMAGE AVAILABLE]

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424/185.1; 530/327, 806, 829 [IMAGE AVAILABLE]

28. 5,534,256, Jul. 9, 1996, Haemophilus somnus outer membrane protein extract enriched with iron-regulated proteins; Andrew A. Potter, et al., 424/184.1, 193.1, 203.1, 236.1, 255.1, 256.1, 278.1, 282.1 [IMAGE AVAILABLE]

29. 5,532,348, Jul. 2, 1996, E6 associated protein and methods of use thereof; Jon M. Huibregtse, et al., 536/23.5; 435/235.1 [IMAGE AVAILABLE]

30. 5,492,825, Feb. 20, 1996, Mammalian inward rectifier potassium channel cDNA, IRK1, corresponding **vectors**, and transformed cells; Lily Y. Jan, et al., 435/352, 69.1, 252.31, 254.11, 320.1; 536/23.5 [IMAGE AVAILABLE]

31. 5,470,734, Nov. 28, 1995, Recombinant herpesvirus of turkeys and live **vector** vaccines derived thereof; Paulus J. A. Sondermeijer, et al., 424/229.1, 211.1, 214.1, 816; 435/235.1; 536/23.72 [IMAGE AVAILABLE]

32. 5,468,845, Nov. 21, 1995, Antibodies to osteogenic proteins; Hermann Oppermann, et al., 530/387.9, 350 [IMAGE AVAILABLE]

33. 5,462,925, Oct. 31, 1995, Transforming growth factor .beta.2,3; Yasushi Ogawa, et al., 514/12; 530/324, 350, 399; 930/10, 120 [IMAGE AVAILABLE]

34. 5,354,664, Oct. 11, 1994, DNA encoding a human thrombomodulin having a modified glycosaminoglycan (GAG) binding site; Takeshi Doi, et al., 435/69.1, 320.1, 348, 357, 358, 367, 372; 530/381; 536/23.1, 23.5 [IMAGE AVAILABLE]

35. 5,354,557, Oct. 11, 1994, Osteogenic devices; Hermann Oppermann, et al., 424/423, 422, 424, 426 [IMAGE AVAILABLE]

36. 5,273,962, Dec. 28, 1993, Human urinary thrombomodulin with a modified glycosaminoglycan (GAG) binding site; Takeshi Doi, et al., 514/8; 435/69.1, 69.3; 514/2; 530/380, 381 [IMAGE AVAILABLE]

37. 5,266,683, Nov. 30, 1993, Osteogenic proteins; Hermann Oppermann, et al., 530/326, 327, 328, 350, 395, 840 [IMAGE AVAILABLE]

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=> d l1,8,13,cit,ab

8. 5,707,618, Jan. 13, 1998, **Adenovirus vectors** for gene therapy; Donna Armentano, et al., 424/93.21, 93.2; 435/172.3, 320.1; 514/44 [IMAGE AVAILABLE]

US PAT NO: 5,707,618 [IMAGE AVAILABLE] L1: 8 of 38

ABSTRACT:
The present invention relates to novel **adenovirus vectors** for use in gene therapy which are designed to prevent the generation of replication-competent **adenovirus** (RCA) during in vitro propagation and clinical use. The invention also provides methods for the production of the novel virus **vectors**. These **vectors** maximize safety for clinical applications in which **adenovirus vectors** are used to transfer genes into recipient cells for gene therapy.

13. 5,670,488, Sep. 23, 1997, **Adenovirus vector** for gene

therapy; Richard J. Gregory, et al., 514/44; 424/93.2; 435/320.1; 935/62
[IMAGE AVAILABLE]

US PAT NO: 5,670,488 [IMAGE AVAILABLE] L1: 13 of 38

ABSTRACT:
Gene Therapy **vectors**, which are especially useful for cystic fibrosis, and methods for using the **vectors** are disclosed.

=> d clms,l1,8,13

US PAT NO: 5,707,618 [IMAGE AVAILABLE] L1: 8 of 38

CLAIMS:

CLMS(1)

We claim:

1. A recombinant **adenovirus vector** having a deleted E1 region of the **adenovirus** genome, into which a heterologous gene has been inserted, and in which the **protein IX** gene has been relocated in the **adenovirus** genome to a location thereof other than the location in which said **protein IX** gene normally resides, such that generation of replication-competent **adenoviruses** is minimized or eliminated.

CLMS(2)

2. The **vector** of claim 1 in which one or more open reading frames of the E4 region is deleted.

CLMS(3)

3. The **vector** of claim 2, in which the **protein IX** gene is relocated to the E4 region.

CLMS(4)

4. The **vector** of claim 2, in which ORF6 of the E4 region is retained.

CLMS(5)

5. The **vector** of claim 4, in which the **protein IX** gene is inserted adjacent to the ORF6 gene.

CLMS(6)

6. The **vector** of claim 1, in which the heterologous gene is a gene encoding CFTR.

CLMS(7)

7. The **vector** of claim 1 in which the heterologous gene is operably linked to a eucaryotic promoter, so as to allow for expression of the gene.

CLMS(8)

8. The **vector** of claim 1, in which the **adenovirus** is selected from among **adenovirus** serotypes 2, 4, 5 and 7.

US PAT NO: 5,670,488 [IMAGE AVAILABLE] L1: 13 of 38

CLAIMS:

CLMS(1)

We claim:

1. An **adenoviral vector** comprising an **adenovirus** genome from which one or more of the E4 open reading frames has been deleted, but retaining sufficient E4 sequences to promote virus replication in vitro, and additionally comprising a DNA sequence of interest operably linked to expression control sequences and inserted into said **adenoviral** genome.

CLMS(2)

2. The **vector** of claim 1 wherein a PGK promoter is operably linked to the DNA sequence of interest.

CLMS(3)

3. The **vector** of claim 1 from which the Ela and Elb regions of the **adenovirus** genome have been deleted.

CLMS(4)

4. The **vector** of claim 1 from which the E3 region of the **adenovirus** genome has been deleted.

CLMS(5)

5. The **adenoviral vector** of claim 1 in which open reading frame 6 of the E4 region is retained in the **adenovirus** genome.

CLMS(6)

6. The **adenoviral vector** of claim 1 in which open reading frame 3 of the E4 region is retained in the **adenovirus** genome.

CLMS(7)

7. The **adenoviral vector** of claim 1 wherein the DNA sequence encodes cystic fibrosis transmembrane regulator protein.

CLMS(8)

8. The **adenoviral vector** of claim 2 wherein the DNA sequence encodes cystic fibrosis transmembrane regulator protein.

CLMS(9)

9. The **adenoviral vector** of claim 3 wherein the DNA sequence encodes cystic fibrosis transmembrane regulator protein.

CLMS(10)

10. The **adenoviral vector** of claim 3 wherein the DNA sequence is inserted into the deleted Ela and Elb regions of the **adenoviral** genome.

CLMS(11)

11. The **adenoviral vector** of claim 5 wherein the DNA sequence encodes cystic fibrosis transmembrane regulator protein.

CLMS(12)

12. The **adenoviral vector** of claim 6 wherein a cytomegalovirus promoter is operably linked to the DNA sequence of interest.

CLMS(13)

13. A method for providing cystic fibrosis transmembrane conductance regulator protein to airway epithelial cells of a cystic fibrosis patient comprising administering directly to airway epithelial cells of the patient an **adenoviral vector**, said **vector** comprising an **adenovirus** genome from which one or more E4 open reading frames has been deleted, but retaining sufficient E4 sequences to promote virus replication in vitro, and additionally comprising a DNA sequence encoding cystic fibrosis transmembrane regulator protein operably linked to expression control sequences and inserted into the E1 region said **adenoviral** genome, under conditions whereby the DNA sequence encoding cystic fibrosis transmembrane regulator protein is expressed and a functional chloride ion channel is produced in the airway epithelial cells of the patient.

CLMS(14)

14. The method of claim 13 wherein open reading frame 6 of the E4 region of the **adenovirus** genome is retained in the **vector**.

CLMS(15)

15. The method of claim 13 wherein the expression control sequences operably linked to the DNA sequence comprise the PGK promoter.

CLMS(16)

16. The method of claim 13 in which the Ela and Elb regions of the **adenovirus** genome of the **vector** have been deleted.

CLMS(17)

17. The method of claim 13 in which the E3 region of the **adenovirus** genome of the **vector** has been deleted.

CLMS(18)

18. The method of claim 13 wherein open reading frame 3 of the E4 region of the **adenovirus** genome is retained in the **vector**.

CLMS(19)

19. The method of claim 18 wherein the expression control sequences operably linked to the DNA sequence comprise a cytomegalovirus promoter.